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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,112	08/23/2001	Stephen Donovan	D-2875DIV.	1929

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EXAMINER

KAM, CHIH MIN

ART UNIT	PAPER NUMBER
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1653

10

DATE MAILED: 01/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/938,112

Applicant(s)

DONOVAN, STEPHEN

Examiner

Chih-Min Kam

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-25, 36, 37 and 67-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 21, 22, 36, 37, 67-75, 77 and 78 is/are allowed.
- 6) ☒ Claim(s) 23-25, 76, 79 and 80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. A reference (US Patent 6, 632,440 B1) relevant to the examination of the instant application is now available, and the pending claims are examined upon expiration of the suspension of the application.

Status of the Claims

2. Claims 21-25, 36, 37 and 67-80 are pending.

Applicants' amendment filed on April 15, 2003 (Paper No. 8) is acknowledged.

Applicant's response has been fully considered. Claims 21, 23, 36, 37, 67-72 and 76-80 have been amended. Therefore, claims 21-25, 36, 37 and 67-80 are examined.

Objection Withdrawn

3. The previous objection of claim 76 is withdrawn in view of applicant's amendment to the claim in Paper No. 8.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 21-25, 36, 37, 67-75, 77, 79 and 80 under 35 U.S.C.112, first paragraph, is withdrawn in view of applicant's amendment to the claim, and applicant's response at page 5 in Paper No. 8.

5. The previous rejection of claims 21-25, 36, 37 and 67-80 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicant's amendment to the claim, and applicant's response at page 6 in Paper No. 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 76 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for obtaining an agent for alleviating pain, the method comprising producing a genetic construct having nucleic acids encoding a botulinum toxin, wherein H_C is removed or modified to reduce its ability to bind to receptors at the neuromuscular junction, and covalently attaching the modified botulinum toxin to a targeting moiety of substance P, does not reasonably provide enablement for a method for obtaining an agent for alleviating pain, the method comprising producing a genetic construct having nucleic acids encoding a botulinum toxin, and covalently attaching the botulinum toxin to substance P, where the removal or modification of the H_C of the botulinum toxin is not indicated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 76 encompasses a method for obtaining an agent for alleviating pain, the method comprising producing a genetic construct having nucleic acids encoding a botulinum toxin and covalently attaching the botulinum toxin to substance P. The specification, however, only discloses cursory conclusions (page 18) without data supporting the findings, which state that the agent for alleviating pain comprising a recombinant fusion protein of a clostridial neurotoxin or a clostridial neurotoxin component and a targeting moiety, or comprising a recombinant clostridial neurotoxin component chemically coupled to a targeting moiety. There are no indicia that the present application enables the full scope in view of the method of making the agent comprising a botulinum toxin and a targeting moiety as discussed in the stated rejection. The present

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application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the botulinum toxin where the removal or modification of the H_C of the botulinum toxin is not indicated, which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

There is no working example indicating the claimed method in association with the variants. Example 1 merely indicates the coupling of L chain from botulinum toxin B and H_N chain from botulinum toxin A to produce LH_N, and the agent comprising the clostridial neurotoxin fragments can be produced by recombinant technique.

(3). The state of the prior art and relative skill of those in the art:

The related art (Johnson et al., U. S. Patent 5,955,368) teaches a system to express clostridial gene construction in a clostridial host, which includes a plasmid being transferred from *E. coli* into clostridium species, and a useful host strain permitting high levels of expression of clostridial genes using the clostridial promoter. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide

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specific guidance on the making/use of the agent containing unmodified botulinum toxin covalently attached to substance P, and the effect of the agent to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a method for making an agent for alleviating pain, and the agent comprises a botulinum toxin expressed recombinantly and chemically coupled to and substance P. The specification only indicates recombinant techniques are used to produce an agent comprising substance P and a clostridial neurotoxin, wherein H_C is removed or modified to reduce its ability to bind to receptors at the neuromuscular junction, e.g., an agent of LH_N and substance P (pages 23 and 30-31). However, the specification has not shown the making of an agent containing a botulinum toxin having H_C chain and substance P, and the use of this agent for treating pain. There are no working examples indicating the claimed method. Furthermore, the specification has not demonstrated the effect of the agent in the treatment of pain. Since the specification fails to provide sufficient guidance on the structural variation and the effect of agent containing the botulinum toxin and substance P, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the agent.

(5). Predictability or unpredictability of the art:

The claim is directed to the preparation of an agent containing a botulinum toxin covalently attached to substance P for alleviating pain, however, the specification has not demonstrated the effect of the agent. Since the claims encompass many structural variants, the invention is unpredictable regarding the making and the effect of the agents.

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(6). Nature of the Invention

The scope of the claim includes structural variants in the agent for alleviating pain, but the specification does not identify these variations in the botulinum toxin, nor demonstrates the effect of the agent. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed method associated with variants, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the agents in alleviating pain.

In response, applicants indicate the claims have been amended to a clostridial neurotoxin where the H_C has been removed or modified to reduce its ability to bind to receptors at the neuromuscular junction and to substance P as the targeting moiety. The response has been considered, however the argument is not fully persuasive because claim 76 does not cite the H_C of botulinum toxin has been removed or modified to reduce its ability to bind to receptors at the neuromuscular junction, thus the rejection of this claim remains, while the rejection of claims 21-25, 36, 37, 67-75 and 77-80 is withdrawn because these claims have been amended to include the limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 23-25 and 79-80 are rejected under 35 U.S.C. 102(e) as being anticipated by Quinn *et al.* (U.S. Patent 6,632,440 B1, priority date August 25, 1999).

Quinn *et al.* teach an agent that inhibits exocytosis in mucus secreting cells or neurons that control or direct mucus secretion, and the agent, which contains a first domain comprising a clostridial toxin light chain or a functional fragment, a second domain comprising the functional domain of the H_N of a clostridial toxin heavy chain, but lacking the functional domain of a clostridial toxin H_C domain, and a third domain, a targeting moiety such as substance P or VIP, that binds to the target mucus secreting or neurons that control mucus secretion, is prepared by covalently linking a clostridial neurotoxin, or a hybrid of two clostridial neurotoxins, in which H_C region of the H-chain has been removed or modified, to a targeting moiety (column 2, line 36-column 6, line 57), e.g., the preparation of the conjugate of substance P and LH_N of botulinum toxin A (Example 1). The reference also indicates the agent can be expressed recombinantly as a fusion protein which includes the targeting moiety in addition to the desired spacer region (claims 24 and 80), and the recombinantly expressed agent may be obtained from the gene encoding one serotype of neurotoxin, or may be obtained from genes encoding one or more serotypes (column 5, lines 23-28; column 6, lines 58-67; claims 23, 25 and 79). The term

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“for alleviating pain” is an intended use, which does not play weight in the patentability of the claimed method of obtaining the agent.

Conclusion

7. Claims 23-25, 76, 79 and 80 are rejected. It appears that claims 21, 22, 36, 37, 67-75, 77 and 78 are free of prior art and allowable.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. *CYK*
Patent Examiner

January 13, 2004


ROBERT A. WAX
PRIMARY EXAMINER